

RESEARCH LETTER

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Basophil activation test in the diagnosis of hypersensitivity reactions to quinolones in a real-life setting

To the Editor,

Quinolones are a family of antibiotics containing a bicyclic core structure related to the compound 4-quinolone and have presented an increased use because of their high potency, broad spectrum of activity, convenient formulations, as well as a comparatively low incidence of side effects.¹⁻³ However, quinolones are the second most common antibiotic class associated with drug hypersensitivity reactions (DHR),³ being the fourth cause of consultations due to suspected drug allergy in Spain, and showing an increased incidence in the last years (4.3% of consultations in 2015 vs 1% in 1992).⁴

Allergic reactions to quinolones can be classified as IgE-mediated immediate reactions (IR) if they appear within 1 hour after drug intake, and T-cell-mediated nonimmediate reactions (NIR) if they appear more than 1 hour after drug intake.^{5,6}

Current European guidelines⁵ for in vitro tests in the diagnosis of DHR indicate that the basophil activation test (BAT) can be recommended for diagnosing IgE-mediated allergy to fluoroquinolones although different studies have shown discordant results.⁶ A high rate of cross-reactivity among different quinolones has been described.^{6,7}

We conducted a retrospective review of patient's clinical histories in a real-life setting, in whom BAT to quinolones was performed, from April 2015 to October 2018 at a tertiary hospital (La Paz University Hospital, Madrid, Spain). Data were collected from clinical histories as part of the routine clinical practice; therefore, ethical approval was not sought for the present study. Patient's consent was not required for this research. The study was conducted according to the Declaration of Helsinki. DHRs were classified by severity, using the grading system for generalized hypersensitivity reactions proposed by Brown et al,⁸ from mild (grade 1) when the reaction comprised skin and subcutaneous tissues only, moderate (grade 2) when features suggest respiratory, cardiovascular or gastrointestinal involvement, to severe (grade 3) when hypoxia, hypotension, or neurologic compromise was associated.

The allergy workup included compatible clinical history, skin testing (prick, intradermal, and/or epicutaneous tests), BAT, and, for some mild cases, drug provocation tests (DPT).

Skin prick tests (SPT) were performed using ciprofloxacin (at 1 mg/ml), levofloxacin (at 5 mg/ml), norfloxacin (one tablet of 400 mg suspended in NaCl), and moxifloxacin (one tablet of 400 mg suspended in NaCl). Intradermal test was performed in one patient

with ciprofloxacin (at 0.001 mg/ml). Epicutaneous tests were performed using fluoroquinolones at 30% with petrolatum.

Basophil activation test was performed incubating 100 µl of heparinized blood with 2, 0.2, and 0.1 mg/ml fluoroquinolones. Negative and positive controls were included by incubating the blood without drug and 20 µl (10 mg/ml) anti-IgE (BD Bioscience), respectively. Samples were stained with anti-CD63-FITC/CD123-PE/Anti-HLA-DR-PerCP (BD Biosciences) and acquired in a FACSCanto II (BD Bioscience). Basophil activation was determined by CD63 up-regulation, and results were considered as positive when the percentage of activated basophils was ≥5% and the stimulation index (SI; ratio between the percentage of activated basophils by drugs and the unstimulated samples) was ≥2 in at least one of the dilutions.¹⁻³

We studied nineteen patients with a clinical history compatible with DHR to different quinolones (Table 1) and compared their clinical features according to BAT results (Table 2). Fifteen (79%) were women, and the mean age was 58 years. The most common quinolone involved in the allergic reaction was levofloxacin ($n = 7$), followed by ciprofloxacin ($n = 6$) and moxifloxacin ($n = 6$); and the severity of the reaction was grade 1 ($n = 10$), grade 2 ($n = 7$), and grade 3 ($n = 2$). Levofloxacin ($n = 5$) and ciprofloxacin ($n = 4$) were the drugs more frequently related with mild reactions. Moxifloxacin was related with more severe reactions (55% of grade 2 and 3 reactions).

Nine (47%) patients presented a positive BAT result, four (44%) for the culprit quinolone and five (56%) for a different quinolone. The other 10 (53%) had a negative BAT result. When moxifloxacin was the quinolone involved in the reaction, the positive BAT result increased to 83% (5/6) of the cases.

Among patients presenting an immediate-type reaction (79%), the BAT was negative in 7 (47%) patients and positive in 8 (53%). Two patients (11%) presented a nonimmediate reaction (>1 hour), one of these had a positive BAT result. In 15 (79%) patients a SPT test was performed, with negative results in all of them. The median time interval between the reaction and the study was 4 months (interquartile range [IQR] = 3–7).

Among the 10 (53%) patients with mild DHR, 6 (60%) had a negative BAT result and 4 (40%) a positive result (2 to the suspected quinolone and 2 to a different one). Among the 9 (47%) patients with anaphylactic reactions (grades 2 and 3), 4 (44%) had a negative BAT and 5 (56%) had a positive one.

For safety and ethical reasons DPT was contraindicated in patients that presented anaphylactic reactions (grade 2 and 3). We

TABLE 1 Demographical, clinical, and biological characteristics of the patients who developed hypersensitivity reactions to quinolones studied with basophil activation test

N°	Age (y)/ Sex	Drug involved	Severity (grade)	Interval between drug and reaction	Interval between reaction and study (months)	Total IgE (kU/L)	BAT Quinolone	Result	BAT CD63 (%)	Skin prick test	Drug provocation test
1	42/M	MOX	3	Imm	48	146	CIP MOX	Pos Neg	15.8 0.6	NP NP	NP
2	22/F	LEV	1	Imm	5	250	CIP LEV MOX	Neg Neg Pos	1.4 3.7 6	Neg Neg NP	NP
3	50/F	MOX	2	45 min	3	15.6	CIP LEV MOX NOR	Neg Neg Neg Pos	1.7 2.4 2.3 18.7	NP NP Neg NP	NP
4	68/F	MOX	2	4 hours	3	<2	CIP LEV MOX	Neg Neg Pos	0.9 0.9 6.1	NP Neg ^a Neg ^a	NP
5	44/F	CIP	2	15 min	7	Unk	CIP LEV MOX	Neg Neg Pos	1.2 1.1 5.8	Neg Neg Neg	NP
6	62/F	MOX	1	30 min	7	279	CIP LEV MOX	Neg Neg Pos	1.2 1.8 5	Neg NP Neg	NP
7	85/M	LEV	1	Imm	3	883	CIP LEV MOX	Neg Pos Neg	2.7 5.4 1.2	Neg Neg Neg	NP
8	45/F	MOX	3	60 min	2	Unk	CIP LEV MOX	Neg Neg Pos	2.2 0.9 5	Neg Neg Neg	NP
9	58/F	LEV	1	5 min	3	Unk	CIP LEV MOX NOR	Neg Neg Neg Pos	2.6 2.4 3 10	NP NP NP NP	NP
10	29/F	LEV	1	15 min	5	Unk	CIP LEV MOX	Neg Neg Neg	0.9 1.7 4.3	Neg Neg Neg	Positive (involved quinolone, LEV)
11	41/F	LEV	1	8 hours	3	Unk	CIP LEV	Neg Neg	0.6 0.4	Neg Neg	Negative (alternative quinolone)
12	65/F	LEV	2	15 min	24	Unk	LEV MOX	Neg Neg	1.3 3.3	Neg NP	NP

(Continues)

TABLE 1 (Continued)

N°	Age (y)/ Sex	Drug involved	Severity (grade)	Interval between drug and reaction	Interval between reaction and study (months)	Total IgE (kU/L)	BAT Quinolone	Result	BAT CD63 (%)	Skin prick test	Drug provocation test
13	52/M	CIP	1	30 min	3	27	CIP LEV MOX	Neg Neg Neg	2.2 1.2 1.1	Neg NP NP	NP
14	39/F	MOX	2	30 min	6	Unk	CIP LEV MOX	Neg Neg Neg	3 1.7 3.5	Neg Neg Neg	NP
15	85/M	CIP	1	Imm	Unk	819	CIP	Neg	1.7	Neg ^{a,b}	Negative (alternative quinolone)
16	77/F	CIP	1	Unk	3	Unk	CIP	Neg	1.7	Neg	Negative (alternative quinolone)
17	87/F	CIP	1	Unk	12	3.54	CIP LEV	NV Neg	- 0.7	NP NP	Negative (involved quinolone, CIP) Negative (alternative quinolone)
18	70/F	LEV	2	20 min	7	Unk	CIP LEV MOX	Neg Neg Neg	1.3 0.6 2.7	Neg Neg Neg	NP
19	74/F	CIP	2	30 min	3	Unk	CIP LEV	Neg Neg	1.2 0.8	Neg Neg	Negative (involved quinolone, CIP)

Abbreviations: CIP, Ciprofloxacin; F, Female; Imm, Immediate reaction; LEV, Levofloxacin; M, Male; MOX, Moxifloxacin; Neg, Negative; NOR, Norfloxacin; NP, Not performed; NV, Not valuable; Pos, Positive; Unk, Unknown.

^aNegative epicutaneous test.

^bNegative intradermal test.

TABLE 2 Clinical features according to BAT results

	Total (n = 19)	BAT positive (n = 9)	BAT negative (n = 10)
Age, mean (range) (years)	57.6 (22-87)	52.9 (22-85)	61.9 (29-87)
Gender (male/female)	4/15	2/7	2/8
Culprit drug			
Ciprofloxacin (n, %)	6/19 (31.6%)	1/6 (16.7%)	5/6 (83.3%)
Levofloxacin (n, %)	7/19 (36.8%)	3/7 (42.9%)	4/7 (57.1%)
Moxifloxacin (n, %)	6/19 (31.6%)	5/6 (83.3%)	1/6 (16.7%)
Severity of the reaction			
Grade 1 (n, %)	10/19 (52.6%)	4/10 (40%)	6/10 (60%)
Grade 2 (n, %)	7/19 (36.8%)	3/7 (42.9%)	4/7 (57.1%)
Grade 3 (n, %)	2/19 (10.5%)	2/2 (100%)	0/2 (0%)
Grade 2 and 3 (n, %)	9/19 (47.4%)	5/9 (55.6%)	4/9 (44.4%)
Time until reaction			
Immediate-type reaction (<1 h) (n, %)	15/19 (78.9%)	8/15 (53.3%)	7/15 (46.7%)
Accelerated reaction (>1 h) (n, %)	2/19 (10.5%)	1/2 (50%)	1/2 (50%)
Unknown (n, %)	2/19 (10.5%)	0/2 (0%)	2/2 (100%)
Time between the reaction and the study, median (Q1-Q3) (months)	4 (3-7)	3 (3-7)	5 (3-7)
Positive Skin prick test (n, %)	0/15 (0%)	0 (0%)	0 (0%)
Drug Provocation Test (DPT) (n, %)	6/19 (31.6%)		
Positive DPT	1/6 (16.7%)	0 (0%)	1/6 (16.7%)
Negative DPT	5/6 (83.3%)	0 (0%)	5/6 (83.3%)

performed DPT if ST and BAT were negative. From the 10 patients with mild reactions (grade 1), three had presented a positive BAT result and one patient chose to not be studied with DPT. We finally performed DPT in 6 of these patients with the suspected quinolone (n = 4) or with an alternative quinolone (n = 2). Patient 10 presented a cutaneous reaction after the DPT with the culprit quinolone (levofloxacin). She had presented an initial grade 1 reaction and the allergic study had shown a negative result of SPT and BAT. The other 5 (83%) patients showed good tolerance to DPT with quinolones.

Previous studies have reported discordant results about the helpfulness of BAT for the diagnosis of DHR to quinolones.⁷ Moreover, it has clearly shown a greater usefulness than skin testing, as it was demonstrated in our study and has been published before.^{3,7,9}

Seitz et al¹ described no positive results in a small series of 4 patients with immediate DHR to quinolones. Ben Said et al⁹ found a positive BAT result in all patients studied (n = 5) which had presented an anaphylactic reaction. In line with our results, Rouzaire et al¹⁰ described the excellent negative predictive value of BAT in the care of patients with a significant clinical history of immediate-type reactions to quinolones. They performed a DPT in 15 patients that had a negative result of BAT, with good tolerance of the culprit drug readministration.

Our findings are concordant with previous researches, although the small size of patients does not allow to estimate BAT sensitivity and specificity in this study. BAT sensitivity to quinolones has not been clearly established, but some studies^{2,3} have described a positive result greater than 70% of the cases studied. They also found a higher rate of positive results for anaphylactic reactions^{2,3} and when moxifloxacin was the culprit drug¹¹ which is consistent with our results.

In conclusion, BAT to quinolones seems to be helpful in the diagnosis of drug allergy, being of great value in comparison to ST even in mild DHR. BAT was especially useful when the DHR were more severe (56% positive BAT vs 40%) and when moxifloxacin was the drug involved. In our study, a negative BAT was a valuable tool in the decision to perform DPT and find alternative quinolones. Further studies will help to corroborate the usefulness of this test.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

DLA contributed to data collection, drafted the manuscript, and coordinated edits on the final version. FVS, contributed to data collection and the development of the manuscript. MGM performed the basophil activation test, revised, and edited the manuscript. RC, AF,

MLB, and JDO selected patients, revised, and edited the manuscript. The final version of the manuscript was approved by all authors.

DECLARATION

Data were collected from clinical histories as part of the routine clinical practice therefore ethical approval was not sought for the present study. Patient's consent was not required for this research. The study was conducted according to the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

David Loli-Ausejo¹ 

Francisca Vélchez-Sánchez¹ 

Rosario Cabañas^{1,2} 

Ana Fiandor^{1,2} 

Magdalena Lluch-Bernal^{1,2} 

Miguel González-Muñoz^{2,3} 

Javier Domínguez-Ortega^{1,2} 

¹Allergy Department, La Paz University Hospital, Madrid, Spain

²Hospital La Paz Institute for Health Research (IdiPAZ, Madrid, Spain

³Immunology Department, La Paz University Hospital, Madrid, Spain

Correspondence

David Loli-Ausejo, Allergy Department, La Paz University Hospital, Paseo de la Castellana 261, Madrid 28046, Spain.

Email: David.loli.ausejo@gmail.com

ORCID

David Loli-Ausejo  <https://orcid.org/0000-0002-6282-0122>

Francisca Vélchez-Sánchez  <https://orcid.org/0000-0002-3735-6129>

Rosario Cabañas  <https://orcid.org/0000-0001-8601-1728>

Ana Fiandor  <https://orcid.org/0000-0003-0446-9562>

Magdalena Lluch-Bernal  <https://orcid.org/0000-0002-5815-5211>

Miguel González-Muñoz  <https://orcid.org/0000-0002-3957-4955>

Javier Domínguez-Ortega  <https://orcid.org/0000-0002-5397-2327>

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